Flow-related techniques for preoperative goal-directed fluid optimization

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Background. Improved postoperative outcome has been demonstrated by perioperative maximization of cardiac stroke volume (SV) with fluid challenges, so-called goal-directed therapy. Oesophageal Doppler (OD) has been the most common technique for goal-directed therapy, but other flow-related techniques and parameters are available and they are potentially easier to apply in clinical practice. The objective of this investigation was therefore to use OD for preoperative SV maximization and compare the findings with a Modelflow determined SV, with an OD estimated corrected flow time (FTc), with central venous oxygenation (S\textsubscript{vO}2) and with muscle and brain oxygenation assessed with near infrared spectroscopy (NIRS).

Methods. Twelve patients scheduled for radical prostatectomy were anaesthetized before optimization of SV estimated by OD. A fluid challenge of 200 ml colloid was provided and repeated if at least a 10% increment in OD SV was obtained. Values were compared with simultaneously measured values of Modelflow SV, FTc, S\textsubscript{vO}2 and muscle and cerebral oxygenation estimated by NIRS.

Results. Based upon OD assessment, optimization of SV was achieved after the administration of 400–800 ml (mean 483 ml) of colloid. The hypothetical volumes administered for optimization based upon Modelflow and S\textsubscript{vO}2 differed from OD in 10 and 11 patients, respectively. Changes in FTc and NIRS were inconsistent with OD guided optimization.

Conclusion. Preoperative SV optimization guided by OD for goal-directed therapy is preferable compared with Modelflow SV, FTc, NIRS and S\textsubscript{vO}2 until outcome studies for the latter are available.

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Hypovolaemia and a perioperative fluid overload are deleterious for organ function and, therefore, for recovery from surgery.1 2 In this context an individualized optimization strategy has been proposed in which flow-related parameters such as cardiac stroke volume (SV) are used to guide fluid therapy, so-called individualized goal-directed therapy.2 Within this concept individual differences as gender, age, co-morbidity, body composition and hydration are taken into account, while the use of a fixed volume regimen, or achievement of predefined haemodynamic values, does not appreciate such individual differences. Perioperative goal-directed therapy has been demonstrated to improve outcome by enhancing gastrointestinal functional recovery and reducing postoperative nausea and vomiting, morbidity and hospital stay.2–6

The most used monitor in goal-directed therapy has been the oesophageal Doppler (OD), but other modalities such as Modelflow-derived SV, muscle and cerebral oxygenation (S\textsubscript{mO}2 and S\textsubscript{CO}2) determined by near infrared spectroscopy (NIRS) and central venous oxygenation (S\textsubscript{vO}2) are available and may be easier to apply in daily clinical practice. However, no comparative studies exist to define other techniques for goal-directed therapy. Therefore, the purpose of this study was to compare SV changes derived from OD with changes in OD corrected flow time (FTc), Modelflow-derived SV, S\textsubscript{mO}2, S\textsubscript{CO}2 and S\textsubscript{vO}2 during preoperative goal-directed therapy.
Methods
In a prospective trial 12 patients scheduled for elective radical prostatectomy were studied after informed consent was obtained. In order to correlate values used for optimization, only patients with a positive response to a fluid challenge as assessed by OD were included. A positive response was defined as a 10% increase in OD SV 5 min after administration of 200 ml colloid\(^5\)\(^7\) as previously used in studies with a positive impact on outcome.\(^2\)\(^–\)\(^6\) Patient age was median 62 yr (range, 52–69 yr); weight 83.0 kg (range, 62–98 kg) and height 179.5 cm (range, 174–190). Exclusion criteria were ASA class >II, diabetes, age<18 or >69 yr, oesophageal pathology or refusal to participate in the study. The local ethics committee was consulted regarding approval but, as the trial was considered as a quality assessment of daily practice, no formal assessment and approval were deemed necessary. The trial was registered by the Danish data protection agency (Copenhagen, Denmark) and by ClinicalTrials.gov under the US national library of medicine (NCT00286338).

Before anaesthesia
Patients were allowed to eat solid foods and drink clear fluids up to 6 and 2 h before surgery, respectively. An i.v. line was established in the right hand and flushed with 10 ml of lactated Ringer’s solution. Standard monitoring was applied including non-invasive assessment of blood pressure, pulse oximetry and an ECG recording. Furthermore, a NIRS optode (SAFB-SM, Somanetics Corporation, Troy, USA) was applied over the left biceps muscle and on the forehead to register estimates of muscle (\(S_m\)) and frontal lobe (\(S_{CO_2}\)) oxygenation, respectively.\(^8\) A finger cuff for the measurement of finger blood pressure with the finapres method (Finometer, FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands) was placed on the middle part of third finger of the right hand. By measuring the finger blood pressure, a beat-to-beat SV was obtained.\(^9\) A thoracic epidural catheter was provided (Th 9-12) for postoperative pain treatment and its placement was tested with 3 ml of lidocaine 2% with epinephrine. The catheter was not used until the trial was completed. Values for \(S_m\) and \(S_{CO_2}\), SV Modelflow and standard monitoring were registered before induction of anaesthesia.

During anaesthesia
For induction a remifentanil infusion at 0.5 \(\mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) was initiated and when the patient reported sedation, propofol 2.0 \(\mu \text{g} \cdot \text{kg}^{-1}\) was administered. Oral intubation was facilitated with cisatracurium 0.1 \(\mu \text{g} \cdot \text{kg}^{-1}\). Propofol 0.4–0.5 \(\mu \text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) and remifentanil 0.3–0.5 \(\mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) were used for maintenance of anaesthesia and the set infusion rate was not changed within 15 min before measurements of cardiac performance. In case of a systolic arterial pressure lower than 80 mm Hg, 5–10 mg of ephedrine was administered but never within 15 min of measurements of cardiac performance. A second large bore i.v. line was placed in the left arm and it was flushed with 10 ml lactated Ringer’s solution.

After induction of anaesthesia and with the patient in Trendelenburg’s position, a central venous catheter (PreSep, Central venous oximetry catheter, Edward Lifesciences, Irvine, USA) was placed in the right internal jugular vein under ultrasound guidance. The catheter was connected to a monitor (Vigileo, Edward Lifesciences, Irvine, USA) and calibrated with a blood sample (ABL 825, Radiometer, Copenhagen) obtained after the patient was supine and, subsequently, an online continuous \(SV_{CO_2}\) measurement was available. An OD probe (DPn 240 or ADPn 72, Deltx medical, Chichester, UK) was greased with a lubricant and inserted orally or nasally to the mid-oesophagus where an optimal blood flow signal from the descending aorta was obtained by one investigator. The CardioQ monitor (Deltex medical, Chichester, UK) was used to estimate SV by measuring the flow velocity in the descending aorta. Integration of the velocity over time provides the stroke distance. This distance is transformed into SV by a nomogram taking gender, height and weight into account. The nomogram is based on multiple correlations of SV estimated by thermodilutional technique with a pulmonary artery catheter. The CardioQ was set to integrate SV over five cycles. The CardioQ also estimates the FTC, which is the length of the systole corrected to a HR of 60 bpm. After application of the OD probe and the central venous catheter, SV and FTC estimated by OD and \(SV_{CO_2}\) were registered every minute together with the \(S_m\) and \(S_{CO_2}\) and the Modelflow estimate of SV.

A goal-directed optimization strategy was then used with maximization of SV estimated by OD.\(^5\)\(^7\) A bolus of 200 ml colloid (6% HES 130/0.4, Fresenius Kabi AB, Uppsala, Sweden) was administered over 2 min, and 5 min later the estimated SV was assessed and the procedure was repeated if there was an increase in SV of \(\geq 10\%\) (Fig. 1). When the fluid bolus did not result in a SV increment \(\geq 10\%\), optimization was regarded as achieved, the study was finished and surgery commenced.

Evaluation of fluid administration
When a fluid challenge is provided a choice is made as whether to continue, or to stop fluid administration. The algorithm used with OD was also applied for Modelflow. Maximization of \(SV_{CO_2}\) was used to define normovolaemia,\(^10\) and an increase of 1% after a fluid challenge was considered as justification of another fluid challenge until no further increase was seen.\(^10\) As the principal method chosen for optimization was OD, situations appeared where fluid administration was either stopped before, or continued
after optimization would have been achieved with one or several of the other methods. Data obtained were normalized for representation to a mean time respecting the optimization period (> 10% increment in OD estimated SV after a fluid challenge) and the equilibrium period (< 10% increment OD estimated SV after a fluid challenge).

**Statistic analysis**

As no data were available for power analysis, a number of 12 patients were chosen arbitrarily for the evaluation. A package was used for the statistical analysis of data (SigmaStat, Build 3.0, SPSS Inc., IL) and a $P$-value of < 0.05 was considered statistically significant. To identify...
differences in variables and time, a one-way ANOVA for repeated measurements was used. To identify differences related to time between the SV estimated by OD and Modelflow, respectively, a two-way ANOVA for repeated measurements was used. For post hoc pair-wise multiple comparison analysis, the Tukey test was applied. Graphical data are presented as mean (SEM).

Results

Twelve of 13 screened patients had a positive response to the colloid challenge. To compare the results of these 12 patients, values were normalized to illustrate ‘a typical patient’ (Fig. 2). As the optimization curves of OD SV were regarded as obeying Starling’s law of the heart, equivalent parts of the individual curves, that is only ‘ascending’ and ‘flat’ parts, respectively, were used to construct the mean curves. The mean optimization and equilibrium period was 0–10 and 10–17 min, respectively. Optimization in the 12 patients began a median of 28 min (range, 22–37 min) after induction of anaesthesia. Eight, three and one patient needed 400, 600 and 800 ml of colloid, respectively, for optimization and hence the mean was 483 ml. Mean values for OD SV and Ftc, Modelflow SV, SmO₂, ScO₂ and SvO₂ in patients with a positive fluid response are illustrated and values of MAP and HR.

During optimization no significant changes were seen in MAP (from 62 to 64 mm Hg), but HR decreased from 57 to 52 bpm (P<0.05) (Fig. 2). There were no significant changes in the SmO₂ and ScO₂ values, whereas SvO₂ increased from 77.9 to 80.7% (P<0.05). There was an increase in Ftc although it was not steady throughout the study period. An increase in SV estimated with OD and Modelflow was observed during the optimization period, and without significant difference between the methods. Individual responses are shown in Figure 3. Figure 4 illustrates differences in volumes administered if Modelflow, SvO₂ and SmO₂ were used to guide fluid therapy, compared with OD, which, a priori, was defined as the reference in our study. Overall, volumes differed in 10 and 11 patients if Modelflow and SvO₂, respectively, were used as guides in fluid administration.

Discussion

As Shoemaker and colleagues 11 introduced the concept of ‘supraphysiological haemodynamic values’ in evaluation of patients in shock, extensive research has evaluated the impact of oxygen delivery optimization. Results of optimization of cardiovascular variables as determined by a pulmonary artery catheter have for many reasons been inconsistent. However, a strategy based upon individualized perioperative SV maximization, through fluid challenges, have demonstrated a positive effect on clinical outcome after surgery when using an algorithm as in the present study. 2–6 As the use of similar individualized strategies
Fig 3 Stroke volume (SV) estimated by oesophageal Doppler (OD) and Modelflow (MF) in preoperative fluid optimization for 12 patients with a positive response in OD estimated SV to a fluid challenge (filled circle, OD; open circle, MF).
with other techniques than OD for perioperative goal-directed therapy is limited or non-existing. OD SV was the chosen standard in our study to which other methods were compared.

As expected,12 no significant changes were seen in MAP but HR decreased 5 bpm (9%) after the optimization period. Whether this decrease in HR was a result of the fluid optimization per se or other factors, including anaesthesia, is unknown. Nevertheless, in clinical practice a change in HR of 5 bpm appears trivial and would normally not lead to any interventions. Although the decrease in HR sustains that an optimized state is reached, the reduction in HR became manifest after the optimization period (Fig. 2), also supporting that HR is not a suitable monitor of volume status.

As maximization of \( SVO_2 \) may define ‘normovolaemia’, fluid administration should be continued until \( SVO_2 \) is maximized.10 The advantage of this concept is that \( SVO_2 \), in contrast to SV and CO, is influenced only by haemodilution when haemoglobin concentration is reduced by \( \sim 50\% \).13 Former evaluations have estimated that an increase in \( SVO_2 \) of 1% is achieved by the administration of 100 ml until \( SVO_2 \) is maximized.14,15 The 2.6% increase in \( SVO_2 \) after administration of on average 483 ml therefore suggests that the additional amount needed in six patients (Fig. 4) where a maximal \( SVO_2 \) was not confirmed before OD suggested full optimization, probably was minor. Five patients required less fluid with \( SVO_2 \) measurements than OD but the effect of the different volumes from OD estimation cannot be concluded as no postoperative outcome studies are available to assess the value of \( SVO_2 \) maximization in goal-directed therapy.

No significant changes were seen in \( SmO_2 \) and \( ScO_2 \). Oxygenation in muscle and brain determined by NIRS does therefore not assess the volume requirements as derived by OD (Fig. 4). The volume required as estimated by use of OD correlates with compromised splanchnic perfusion7 which may be different from the volume estimated with \( SmO_2 \) and \( ScO_2 \).

There was a discrepancy between the comparable curves for OD and Modelflow (Fig. 2) and the poor correlation between the apparent choices, which had to be made with these techniques in fluid optimization (Fig. 4). As the increase in SV depends on the starting point, different methods may differ in their choices made after a fluid challenge. In our study we found that the curves derived with Modelflow may fit with OD curves in some patients, but exceptions were found in several patients (Fig. 3), probably contributing to a discrepancy in suggested optimization volume in 10 patients compared with OD (Fig. 4). However, this discrepancy cannot be explained from our data but, as OD is the only outcome-validated method in individualized goal-directed therapy and choices made with the other methods differ, no recommendations on these methods can be given until further evaluation and outcome studies are available. Although the difference in volumes seems minor (Fig. 4), it should be noted that in three and six patients, MF and \( SVO_2 \), respectively, suggested further fluid administration of an unknown magnitude because optimization was guided by OD.

In addition to SV, OD determined FTc, but FTc was not included in the optimization algorithm. Others have used FTc for goal-directed therapy as it is proposed as a marker of preload.16,17 Although FTc is also affected by other factors (e.g. changes in systemic vascular resistance and compromised ventricular function), an FTc below the normal range (330–360 ms) is most often caused by hypovolaemia, which, therefore, must be ruled out by a fluid challenge as we did in all patients. The registered FTc values increased with fluid challenges, but not as pronounced as the SV, and the significant values occurred after the optimization period (Fig. 2). Although confirming that the patients were optimized with an FTc near the normal range, our data do not support recommendation of FTc in perioperative fluid optimization.

The mean amount administered under OD SV guidance was about 500 ml which is of similar magnitude as found in other optimization studies.2–5 The demonstrated volume deficit is functionally important as it may be associated with splanchnic hypoperfusion which is related with a worsened outcome.18 In addition, a deficit of 500–1200 ml can be associated with cerebral hypoperfusion illustrated in conscious subjects where fainting occurs with an incidence in array of 3.8–52% when haemorrhage increases from 440 to 1200 ml.19 By SV optimization, not only is the risk of complications reduced but also the patient is kept safe from the range of deficit where cerebral perfusion becomes compromised.
In goal-directed therapy studies where an individualized strategy was used with positive impact on outcome, at least a 10% increase in SV was a cut-off for further fluid challenge.\textsuperscript{2–6} The 10% increase is an arbitrary value, but argued for two reasons. Firstly, studies made with this strategy have, without exception, shown improved outcome.\textsuperscript{2–6} Secondly, as haemodilution increases CO and SV per se\textsuperscript{13} a demand of a 10% increase in SV minimizes the risk of administrating fluid on the background of the small changes in SV caused exclusively by haemodilution.

Knowledge of spontaneous variations in SV is of importance if used in goal-directed therapy. SV is influenced by positive pressure ventilation and the variation in SV becomes more pronounced with hypovolaemia.\textsuperscript{20} To minimize this bias of natural variation, the parameter chosen for guidance of therapy is integrated over a period of usually five cycles. The shorter the period of integration, the bigger the variation and the risk of bias in changes that could result in fluid administration. However, the ideal integration time frame has not been evaluated neither in relation to spontaneous nor in controlled ventilation.

There may be other limitations to our results. Firstly, the sample size was small but the object of this study was to evaluate the choices made in fluid therapy with different technologies for the individual patient. Secondly, OD is regarded as a standard in clinical practice as it is the mostly validated in clinical outcome studies regarding goal-directed therapy.\textsuperscript{2–6} However, this predominance does not exclude that other methods with other choices may improve outcome even more. Lastly, there are other methods that were not included in this evaluation. Thus, pulse contour analysis with lithium calibration has been evaluated in one individualized goal-directed therapy study,\textsuperscript{4} and therefore may have a potential in the goal-directed therapy.

In summary, preoperative SV optimization guided by OD for goal-directed therapy is preferable compared with Modelflow SV, FTrc, NIRS and $S_{VO_2}$ until outcome studies for the latter are available.

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